

Goals in emergency management in DS

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Disclosure Statement

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Dravet syndrome

- Dravet syndrome (DS) is a devastating genetic epileptic encephalopathy that has been linked to more than >300 *de novo* mutations in a neuronal voltage-gated sodium channel (SCN)
- Children with DS are at a higher risk for episodes of uncontrolled status epilepticus

Ceulemans B, Boel M, Leyssens K, Van Rossem C, Neels P, Jorens PG, Lagae L (2012) Successful use of fenfluramine as an add-on treatment for Dravet syndrome. *Epilepsia* 53:1131-1139

Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O (2005) Severe myoclonic epilepsy in infancy: Dravet syndrome. *Adv Neurol* 95:71-102.

Introduction

- Dravet syndrome is a very severe form of epilepsy, that has deep impact not only on the affected children, their families but also the health care providers due to the unique challenges associated with the management
- Dravet syndrome, as previously called severe myoclonic epilepsy of infancy is drug refractory epilepsy which was first described by Dr. Charlotte Dravet in 1978, because some variability has been observed in the symptomatology, the name was changed to Dravet syndrome in 1989
- In 2001, Clacs et al, alpha-subunit mutation from the neuron specific sodium channel SCN1A

GOALS

- Treatment options in home, EMS and emergency room
- As described by Berten Ceulemans, major goal are
 - Educate parents
 - What to do
 - Whom to contact
 - Where to go

EDUCATION OF FAMILIES

- Most Dravet patients carry a de novo mutation
- Disorder is not the result of an external factor such as vaccinations
- Relapses are common
- Chiron describes reduced mortality rate due to adequate prevention, better seizure treatment and a better choice of anti-epileptic drugs.

Shorvon S, Berg A. Pertussis vaccination and epilepsy an erratic history, new research and the mismatch between science and social policy. Epilepsia 2008; 49: 219–25.

Chiron C. Current therapeutic procedures in Dravet syndrome. Dev Med Child Neurol 2011; 53(Suppl. 2): 16–8.

Education upon initial diagnosis

- A productive communication requires a complex, profound and empathic relationship.
- Medical team have to understand the possible impact of different cultural, psychological, and familial backgrounds; and accept that intervention will require different words for different parents.

Families denial, anger and frustration

- Age at onset of febrile seizures

“Which actually is my child’s disease?”

- “They told me these are only febrile convulsions.”

- “They told me this is a benign epilepsy and that seizures will disappear with age.”

- “I do not believe these are epileptic fits.”

- “We want to know everything about this syndrome.”

- Reactions can be extremely different

- Tiziana Granata, **Comprehensive care of children with Dravet syndrome**, *Epilepsia*, Special Issue: Severe Myoclonic Epilepsy – Dravet Syndrome: Thirty Years Later **Volume 52, Issue Supplement s2, pages 90–94, April 2011**

Is it my fault?

- Above all, the one thing that families need to understand is that it is not their fault.
- In most cases Dravet Syndrome is caused by a gene mutation, which occurs randomly
- Gene mutations happen in everyone. It is simply random when they occur in an important gene like SCN1a

What to do

- Prevention
- Fast and effective treatment of status epilepticus
- Beside parents other people in charge of the children also needs guidelines
 - Caregivers
 - Schools
 - Special centers
 - EMS
 - Emergency rooms
 - Hospitals

Prevention

Reduced mortality rates

- Treat fever
- Avoid hyperthermia
- Avoid Triggers
- Avoid stressful situations

Fever, treatment and prevention

- Need to treat fever aggressively
- It is important to remember that the problems related to infections are much more harmful than possible seizures induced by the vaccinations
- Vaccinations should be performed according to the usual recommendations
- Children with epilepsies including Dravet syndrome patients should grow up as normally as possible

Triggers, seizures and balance in life

- Seizures, may be induced by a vast variety of triggers, including, theoretically, every sensorial stimulus, excitement and stressful situations
 - light
 - visual patterns
 - water, sounds
 - often gratifying circumstances, such as birthday or Christmas parties
- Every family becomes familiar with the specific triggers in their own child and also learns their management; doctors nevertheless must help the family to find a balance between avoiding triggers and avoiding everyday experiences

Treatment in home

- Risk of status epilepticus
- Aggressive use of emergency medications
- The high frequency of seizures, their long duration, and the frequent resistance to diazepam heavily impact everyday life of families.
- Dose of other medications as clonazepam, diazepam, lorazepam and midazolam should also be adjusted according to the child's weight

Proposed guidelines of acute seizure treatment

- Step one: when a major seizure starts, administer oral Clonazepam 0.5–1mg
- Step two: 5 min later, administer oral Clonazepam 0.5–1mg
- Step three: 15 min later or as soon as possible, patient needs to get treatment in emergency room

First Aid-home-school-daycare

- Protect the child's airway.
- If anything is visible in the mouth, gently clear it with a finger to prevent choking.
- Place child on a protected surface and position on side

Don't try to force anything into the child's mouth.

- This is unnecessary and can cut the mouth, injure a tooth, cause vomiting, or result in a serious bite of your finger. Also, bites of the tongue are rare and harmless.
- Don't try to resuscitate the child just because breathing stops momentarily for 5 to 10 seconds. Instead, try to clear the airway. Breathing never looks normal during the seizure, but it's adequate if the color is not bluish.
- Do not try to stop movements by holding tight

First Aid-home-school-daycare

- Give the child an extra dose of anticonvulsants at this time.

Epilepsy Foundation

Neurology, Practice parameter: Treatment of the child with a first unprovoked seizure, Neurology January 28, 2003 vol. 60 no. 2 166-175 ILEA

Practice Guidelines, by subcommittee on Febrile seizures, February, 2011 Pediatrics: February 2011, Volume 127/issue 2J

Child Neurology, 2002 Jan, 17 Supp 1: S44-52

Care beyond home

- Each patient should have a personalized emergency protocol to allow the proper and quick treatment even in different or unfamiliar hospitals.
 - personal protocol
 - demographic data
 - referral physician/hospital contact informationa
 - brief clinical history

Care beyond home

- diagnosis
- allergies
- daily medications
- specific strategies that are known to be effective in an emergency

Tiziana Granata, **Comprehensive care of children with Dravet syndrome, *Epilepsia*, Special Issue: Severe Myoclonic Epilepsy – Dravet Syndrome: Thirty Years Later** [Volume 52, Issue Supplement s2, pages 90–94, April 2011](#)

Care beyond home

- Finally, it might be useful to assemble a portable microenvironment with all the items required for managing seizures, including a rectal diazepam kit, portable oxygen, and daily drugs
- Belgian experience

Nolan K, Camfield CS, Camfield PR. (2008) Coping with a child with Dravet syndrome: insights from families. *J Child Neurol* 23:690–694. [CrossRef](#), [PubMed](#), [Web of Science](#)® Times Cited: 1

Ceulemans B, Boel M, Claes L, Dom L, Willekens H, Thiry P, Lagae L. (2004) Severe myoclonic epilepsy in infancy: toward an optimal treatment. *J Child Neurol* 19:516–521. [CrossRef](#), [PubMed](#), [Web of Science](#)® Times Cited: 22

Emergency Protocols

As Dravet Syndrome is a rare condition it would be unrealistic to expect all medical professionals to know how it presents and how it should be treated, both on a day-to-day basis and in an emergency situation.

Emergency seizure protocol

- UK team strongly recommends for medical team to produce emergency home, ambulance and local hospital protocols
- Detailing the medications to be used when the patient is seizing, the order in which to use them and the appropriate doses (mg/kg).

Dravet syndrome UK team

Ambulance protocol

Detailing the medications which can be used en route to the hospital and information about the measures needed to be taken upon arrival, for example, a resuscitation call being put out

Dravet syndrome UK team

General hospital protocol

- A general hospital protocol would provide some brief information on Dravet Syndrome, any other diagnosis child may have and what tests should be carried out
- They should be on hospital letterhead and signed.
- Once parents have protocols, keep a copy in child's bag at all times, at their school/college/ residence
- All protocols should include child's information, i.e. date of birth, address, current medications, allergies and contact numbers.
- Having emergency protocols that are readily available and accessible can make treating child in an emergency situation a lot easier for everyone concerned

Dravet syndrome UK team

Emergency room protocol

**EMERGENCY ROOM PROTOCOL
SHOULD BE WRITTEN ON NEUROLOGIST'S LETTERHEAD AND SIGNED BY
NEUROLOGIST**

Dear Emergency Personnel,

Have neurologist give an overview of child and seizure history.

*** child is a ... year old that suffers from Dravet syndrome (Severe Myoclonic Epilepsy of Infancy). He frequently has episodes of status epilepticus more than one to two hours. He should be treated quite aggressively in the ER as his seizures are quite difficult to stop and control once they begin.

***Prior to arrival at the ER, he will likely have received rectal valium (Diastat)and/or intranasal versed. Upon arrival if seizures persist, I would recommend treating as follows: List of emergency medications and dosages of what has worked best for child

Dravet Syndrome Foundation

Emergency room protocol

- 1. Medication A mg/kg
- 2. If this does not control seizures, plan on moving on rapidly to a Medication B with a loading dose of mg/kg
- 3. Has failed Medication C and it is in his best interest to move on to more aggressive treatment to control seizures.
- The family is extremely knowledgeable concerning condition and care and will likely be a good guide towards treatment.

Contact me with any questions on further care. Sincerely,

MD (111) 555-1234

More protocols

- Publication in *Epilepsia* Tiziana Granata suggesting
 - A familiar protocol for each member of the family member
 - Plans for second and third option if the first option fails
 - A personalized emergency plan for unfamiliar hospitals
- Personal protocols
 - ❖ Demographic
 - ❖ Physician contact info
 - ❖ Brief history
 - ❖ Diagnosis
 - ❖ Allergies
 - ❖ Medications in use
 - ❖ Medications to use
 - ❖ Medications not to use

Medications not to use in emergency

Sodium channel blockers, worsen seizures associated with Dravet syndrome.

- Phenytoin
- Rufinamide
- Lamotrigine
- Fosphenytoin
- Oxcarbazapine
- Carbamazepine
- Tiagabine
- Vigabatrin

Medications in use

- **Clobazam (0.2-1 mg mg/kg/day)**, part of the standard of care in Europe, is now approved by the FDA in the US. Clobazam is FDA approved for the treatment of seizures in Lennox-Gastaut syndrome

Selmer KK, Lund C, Brandal K, Undlien DE, Brodtkorb E. SCN1A mutation screening in adult patients with Lennox-Gastaut syndrome features. Epilepsy Behav. 2009;16:555-7

Medications in use

- **Stiripentol (30-100 mg/kg/day)** is accepted by epileptologists as an effective therapeutic agent in SCN1A-related seizure disorders. It is part of the early standard of care in Europe, and is used in the US after other conventional anticonvulsants have failed. It is not approved by the FDA for use in the US
In a recent US survey of 82 children with Dravet syndrome, stiripentol was found to be effective in reducing prolonged seizures

Wirrell EC, Laux L, Franz DN, Sullivan J, Saneto RP, Morse RP, Devinsky O, Chugani H, Hernandez A, Hamiwka L, Mikati MA, Valencia I, Le Guern ME, Chancharme L, de Menezes MS. Stiripentol in Dravet syndrome: results of a retrospective U.S. study. *Epilepsia*. 2013;54:1595–604

- **Trials in Europe:**
- Stiripentol, which acts directly on GABA_A receptors, is also a potent inhibitor of the hepatic enzymes CYP3A4, CYP1A2, and CYP2C19. As a result, it increases the serum concentration of several common AEDs, including valproic acid, clobazam, and its metabolite nor-clobazam. Doses above 50 mg/kg/day are usually not tolerated when used in conjunction with valproic acid and clobazam

Thanh TN, Chiron C, Dellatolas G, Rey E, Pons G, Vincent J, Dulac O. *Arch Pediatr*. 2002;9:1120–7. [Long-term efficacy and tolerance of stiripentaol in severe myoclonic epilepsy of infancy (Dravet's syndrome)]

Medications in use

- **Benzodiazepines.** Individuals taking stiripentol must exercise caution in the use of benzodiazepines. A single infusion of diazepam and clonazepam appears to be safe
- **Valproic acid** (10-30 mg/kg/day)

Thanh TN, Chiron C, Dellatolas G, Rey E, Pons G, Vincent J, Dulac O. Arch Pediatr. 2002;9:1120–7. [Long-term efficacy and tolerance of stiripentaol in severe myoclonic epilepsy of infancy (Dravet's syndrome)]

- **Topiramate**

Coppola G, Capovilla G, Montagnini A, Romeo A, Spano M, Tortorella G, Veggiotti P, Viri M, Pascotto A. Topiramate as add-on drug in severe myoclonic epilepsy in infancy: an Italian multicenter open trial. Epilepsy Res. 2002;49:45–8

Medications in use

- **Ethosuximide.** Can be effective for absence seizures. The dose is usually limited by gastrointestinal side effects, which can be minimized by more frequent dosing.
- **Levetiracetam** (20-80 mg/kg/day). Often effective, but may make seizures worse in some individuals

Caraballo RH, Cersósimo R, De los Santos C. Levetiracetam-induced seizure aggravation associated with continuous spikes and waves during slow sleep in children with refractory epilepsies. Epileptic Disord. 2010;12:146–50.

- **Potassium bromide.** Not FDA-approved in the US, but widely used in Japan with reasonable effectiveness

Tanabe T, Awaya Y, Matsuishi T, Iyoda K, Nagai T, Kurihara M, Yamamoto K, Minagawa K, Maekawa K. Management of and prophylaxis against status epilepticus in children with severe myoclonic epilepsy in infancy (SMEI; Dravet syndrome)--a nationwide questionnaire survey in Japan. Brain Dev. 2008;30:629–35.

- **Phenobarbital.** Although effective, phenobarbital is poorly tolerated because of its effects on cognition.
- Phenobarb in SE *Chipaux et al in 2010, unusual consequences of status epilepticus in Dravet syndrome. Seizure 19: 190-194)*

Issues in ER-Bromide

➤ Elevated chloride levels-Bromide therapy

Automated chemistry analyzers may indicate elevated chloride levels because many do not distinguish between halide ions. The usual methods for determining chloride concentrations have an inability to detect differences between chloride and bromide ions.

Therefore, when patients are on bromide therapy, they have elevated chloride levels and may have negative ion gaps

Issues in ER- Benzo and Pheno

- Individuals taking stiripentol must exercise caution in the use of benzodiazepines.
- A single infusion of diazepam and clonazepam appears to be safe
- Phenobarbital when it is taken in combination with stiripentol, the serum concentration of phenobarbital is increased because stiripentol slows the metabolism and excretion of barbiturates.

Ketogenic diet

- Dressler et al has reported that seizures were reduced by more than 50% in 62.5% of persons with Dravet syndrome who stayed on the diet for six months.
- The findings of Nabbout et al in 15 individuals also support the use of the ketogenic diet in Dravet syndrome.

Dressler A, Stöcklin B, Reithofer E, Benninger F, Freilinger M, Hauser E, Reiter-Fink E, Seidl R, Trimmel-Schwahofer P, Feucht M. Long-term outcome and tolerability of the ketogenic diet in drug-resistant childhood epilepsy--the Austrian experience. Seizure. 2010;19:404-8

Nabbout R, Copioli C, Chipaux M, Chemaly N, Desguerre I, Dulac O, Chiron C. Ketogenic diet also benefits Dravet syndrome patients receiving stiripentol: a prospective pilot study. Epilepsia. 2011;52:e54-7

Keto patient in ER-Guidelines

- Look for signs and symptoms of acidosis and hypoglycemia
- Order a Stat BMP and Betahydroxybuterate (BHB)
- CO₂ below 16 treat with either
 - 2-4 ounces of any juice orally or **via GT** and observed for seizures
 - IV bicarb
 - IV Dextrose 5% or 10% small bolus depending on clinical symptoms
- Glucose below 40 treat
 - IV glucose or juice **orally or via GT**
 - Expect a low glucose 45 and above

Do not-for keto in ER

- NO CHEWABLES OR LIQUIDS , CONSIDER THEM AS HAVING ALLERGIES TO GLUCOSE DEXTROSE
- DO not Hang IV Dextrose UNLESS absolutely necessary

To do-for keto in ER

- Ask when was the last meal/feeding
- Determine quickly if the child needs to be NPO if not allow parents to feed as soon as possible
- Advise parents to bring to ER few **meals or prepared formula**

Zebrafish Model of DS

To discover new drug candidates for the treatment of DS, from chemical library of ~1000 compounds, 4 compounds are identified that rescued the behavioral seizure component and out of these two are more promising

- Dimethadione that suppressed associated electrographic seizure activity. This compound blocks neuronal calcium current
- Fenfluramine, also showed antiepileptic activity in zebrafish model. This compound enhances serotonin signaling
- Over 150 compounds resulting in fatality were also identified.

Hope beyond animal model

- In 2007, the reprogramming of adult human dermal fibroblasts into a pluripotent, embryonic stem cell-like state introduced a new source of difficult-to-obtain human tissues, a milestone for regenerative medicine and a novel way to model human diseases
- Moreover, hiPSCs possess the genetic background of the patient, allowing for the creation of disease- or patient-specific cell lines with which to test potential therapeutics with minimal risk to the patient, enabling advances in drug screening in human in vitro models and personalized medicine

Conclusion

Goals in emergency management

- Education: to be mentally prepared for breakthrough sz and status in well controlled child
- Prevention: prevent triggers which might lead to emergencies
- Preparation: for medical team to have emergency guidelines ready and parents to have emergency kit ready
- Action: prevent status by use of benzodiazepines, repeat as needed and extra dose of AEDs as indicated